EXHIBIT A191

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Target Organs for Carcinogenicity of Chemicals and Industrial Exposures in Humans: A Review of Results in the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans

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Abstract

Epidemiological observations indicate that cancers affecting different organs and systems in humans have different causes. At the descriptive level, cancer incidence and mortality rates exhibit patterns of geographic and temporal variation which are distinct and separate for each cancer site and even, at a given site, for different histological types (for instance, increasing squamous cell carcinoma of the lung and decreasing stomach cancer in most developed countries in recent decades). The existence of these distinct patterns in itself indicates that different causes are at the origin of cancers at different sites. Hence, it is of scientific and practical importance not only to identify agents that are carcinogenic to humans but also to specify as definitely as possible the target organ(s) of their action. This is done in the present review of results in the International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.

IARC[2] Monographs Program

A systematic endeavor contributing to the identification of human carcinogens was set up in 1971 by the IARC in the form of a program to evaluate carcinogenic risk of chemicals to humans. The aim of this project is to prepare and publish monographs (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans) (1) in which data on individual chemicals are evaluated: more recently, exposures to complex mixtures have also been considered. To date, 31 volumes have been published, comprising evaluations or reevaluations of 624 chemicals, groups of chemicals, industrial processes, or occupational exposures.

In February 1982, the IARC convened an international Working Group of experts in chemical carcinogenesis and epidemiology to reevaluate the evidence of carcinogenicity to humans for all exposures considered in Vols. 1 to 29 of the IARC Monographs for which some data on carcinogenicity in humans had been reported in the published literature. Reevaluations were made on the basis of studies summarized in the monographs and of all relevant data published subsequently. The results of the meeting have been published as Suppl. 4 to the IARC Monographs (2), which thus provides a synthesis of the evaluation program up to the end of 1981.

Chemicals, groups of chemicals, industrial processes, and occupational exposures were assigned to groups of different levels of evidence of carcinogenicity to humans in a 2-step process: (*a*) on the basis of separate assessments of evidence for carcinogenicity in experimental animals and in humans; and (*b*) on the basis of a combined single evaluation. Assessments of degree of evidence of carcinogenicity are based on the criteria in Table 1.

The combined evaluation and consequent inclusion of a chemical in Group 1, 2 (Subgroups 2A and 2B), or 3 depended on the criteria in Table 2.

Of the exposures evaluated by the Working Group, 7 industrial processes or occupational exposures and 23 chemicals or groups of chemicals were judged to be carcinogenic to humans (Group 1); 61 were adjudged to be probably carcinogenic to humans (Group 2, subdivided into 2 subgroups: 2A, comprising 14 chemicals; and 2B, comprising 47 chemicals). The remaining 64 chemicals, groups of chemicals, industrial processes, and occupational exposures could not be classified as to their carcinogenicity for humans (Group 3).

It is apparent that the definitions given above are exposure oriented and not target organ oriented and that they do not embody provisions to classify exposures according to carcinogenicity for specified target organs. Clearly, for chemicals in Group 1, there must be at least one target organ for which sufficient evidence of carcinogenicity is judged to exist; however, once this level of evidence is reached, *e.g.*, for angiosarcoma of the liver in the case of vinyl chloride, it becomes less critical for rating a compound as carcinogenic to humans whether other organs are affected as well. As a consequence, evaluations by the Working Groups of the target organs affected have been less exhaustive than their evaluations of the overall carcinogenicity of a chemical.

The purpose of this paper, which is the personal responsibility of the six authors, is therefore to complement the evaluations as presented in Suppl. 4 of the Monographs series by adding to the classification of exposures in Group 1, 2, or 3 an indication of their established or (more often) possible target organs.

These indications should prove a useful research tool for epidemiologists, either as pointers to associations between exposures and target organs which need further investigation to be firmly established and quantitated, or as reminders of possible sources of confounding (*e.g.*, benzene, in a study exploring the role of viral factors in leukemias). Other, indirect suggestions with regard to research into carcinogen-target organ relationships may come to epidemiologists from other sources, such as the results of long-term carcinogenicity tests in animals or analysis of body fluids (*e.g.*, evaluation of mutagenicity in urine). Given the intrinsic problems in establishing the target organ(s) of a human carcinogen and the limitations of the present exercise

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[2] The abbreviation used is: IARC, International Agency for Research on Cancer.

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Table 1
Assessment of evidence of carcinogenicity

Degree of evidence	In humans	In experimental animals
Sufficient evidence	A causal relationship between the agent and human cancer is established.	The data show increased incidence of malignant tumors: (*a*) in multiple species or strains; or (*b*) in multiple experiments (preferably with different routes of administration or using different dose levels); or (*c*) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, from short-term tests, or on chemical structure.
Limited evidence	A causal relationship between the agent and human cancer is credible, but other explanations such as chance, bias, or confounding cannot be adequately excluded.	The data suggest a carcinogenic effect but are limited because: (*a*) the studies involve a single species, strain, or experiment; or (*b*) the experiments are restricted by inadequate dose levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (*c*) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (*e.g.*, lung and liver tumors in certain strains of mice).
Inadequate evidence	(*a*) There are few pertinent data; or (*b*) the available studies, while showing evidence of an association, do not exclude chance, bias, or confounding; or (*c*) studies are available which do not show evidence of carcinogenicity.	Because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or, within the limits of the tests used, the chemical was not considered to be carcinogenic.

Table 2
Evaluation of carcinogenicity to humans

Group	Evidence
Group 1, exposure carcinogenic to humans	Evidence of carcinogenicity to humans from epidemiological studies is sufficient.
Group 2, exposure probably carcinogenic to humans	Evidence of carcinogenicity to humans from epidemiological studies ranges from limited to inadequate. To reflect this range, the category is subdivided into higher (Group 2A) and lower (Group 2B) degrees of evidence. Data from studies in experimental animals played an important role in assigning compounds to Category 2, particularly to Group 2B; thus, the combination of sufficient evidence in animals and inadequate evidence in humans usually resulted in a classification of 2B. In a very few cases, the known chemical properties of a compound and the results from short-term tests allowed the classification of a compound to be upgraded (from 3 to 2B or from 2B to 2A).
Group 3, exposure cannot be classified as to its carcinogenicity to humans	Evidence of carcinogenicity to humans and to animals is inadequate to make an evaluation.

(see "Methods" below), the indications presented in Table 3 are appropriate only for use in research.

Identification of Target Organs in Humans

Methods. The 155 chemicals, groups of chemicals, industrial processes, and occupational exposures that were examined by the Working Group which produced Suppl. 4 were reviewed by one of us (F. Merletti), and target organ(s) were provisionally allocated to 3 classes of evidence of carcinogenicity for a given chemical. (For 55 exposures, the epidemiological data were inadequate to specify an association with target organs and were therefore not considered further.) Subsequently, each allocation was subjected to a discussion among the authors; after each chemical had been looked at individually, a final classification was produced. Thus, the classification reflects the consensus of the group; a different group, faced with the same data, might not have produced exactly the same classification.

In preparing both the provisional and the final classification, 3 sources of information were used, as required: (*a*) Suppl. 4; (*b*) individual monographs on the compounds; and (*c*) the original articles in which the epidemiological investigations evaluated in respect of target organs were reported. In deciding whether a chemical should be listed against a certain target organ, the following elements were taken into account: the quality (including assessment of bias and confounding) and number of epidemiological studies suggesting a particular association; the consistency of the reports; and the biological credibility of the association. In general, case reports were not used as evidence for a possible association, unless 3 or more suggested the same association, and/or a rare site was clearly associated with a known exposure. Hypothesis-generating computerized files, such as permanent drug-monitoring systems, were not considered suitable for formulating associations when they represented the only available evidence. Associations between cancer at a specific site and exposure to a drug were usually not considered if exposure to radiation had also been reported. Sites suggested only by single studies were not cited if several larger studies showed no association for that site.

Tab

Target organs for carcinogenicity of chem

Chemical, process, or industry[a]	IARC Monographs ref. (volume and page)	Suppl. 4 ref. (page)	Oral cavity		Gastrointestinal tract						Liver		Nose and nasal sinus						
			Total (140–145)[b]	Salivary gland	Pharynx (146–149)	Total (150–154)	Esophagus	Stomach	Colon	Rectum	Total (155)	Antiosarcoma	Pancreas (157)	Peritoneum (mesothelioma) (158)	Total (160)	Adenocarcinoma	Larynx (161)	Lung, trachea and bronchus (162)	Pleural mesothelioma (163)
Acrylonitrile	*19:* 73	25						Δ[c]										▲	
Adriamycin	*10:* 43	29																	
Aflatoxins	*10:* 51	31									◆								
4-Aminobiphenyl	*1:* 74	37																	
Amitrole	*7:* 31	38																Δ	
Anesthetics, volatile	*11:* 285	41											Δ						
Analgesic mixtures containing phenacetin	*24:* 135	47																	
Arsenic and certain arsenic compounds	*23:* 39	50										▲						◆	
Artificial sweeteners (cyclamate, saccharin)	*22:* 171	97, 224																	
Asbestos	*14:*	52				▲								◆			▲	◆	◆
Auramine	*1:* 69	53																	
Auramine, manufacture of	*1:* 69	53																	
Azathioprine	*26:* 47	55									▲							Δ	
Benzene	*29:* 93	56																	
Benzidine	*29:* 149	57																	
Benzidine-based dyes																			
Direct Black 38	*29:* 295	59																	
Direct Blue 6	*29:* 311																		
Direct Brown 95	*29:* 321																		
Beryllium and beryllium compounds	*23:* 143	60																▲	
N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)	*4:* 119	62																	
Bischloroethylnitrosourea	*26:* 79	63																	
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether	*4:* 231	64																◆	
Bleomycins	*26:* 97	66																	
4-Butanediol dimethanesulfonate (myleran)	*4:* 247	68																	
Cadmium and cadmium compounds	*11:* 39	71			Δ				Δ	Δ								▲	
Carbon tetrachloride	*20:* 371	74									Δ								
Certain combined chemotherapy regimens for lymphomas (MOPP)[d]	*26:* 311	75																	
Chlorambucil	*26:* 115	77																	
Chloramphenicol	*10:* 85	79																	
Chlordane, heptachlor	*20:* 45, 129	80																	
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	*26:* 137	83																	
Chlorinated toluenes, production of																		▲	
Benzal chloride	*29:* 49	84																	
Benzotrichloride	*29:* 73																		
Benzoyl chloride	*29:* 83																		
Benzyl chloride	*29:* 185																		
Chlorophenols (occupational exposure to)	*20:* 349	88																	
Chloroprene	*19:* 131	89				★												★	
Chromium and chromium compounds	*23:* 205	91				Δ									Δ			◆	
Cyclophosphamide	*26:* 165	99																	
2,4-D and esters[e]	*15:* 111	101																	

[a] Tobacco, alcohol, and betel chewing are not included, because they have not yet been evaluated in the Monographs program.
[b] Numbers in parentheses, code numbers of the International Classification of Diseases, 8th revision.
[c] Symbols: Δ, associations only suggested to exist for particular target organs; ▲, target organ-chemical associations judged as possible or plausible to different degrees; ◆, organ-chemical association(s) on which an evaluation of sufficient evidence of carcinogenicity rests; ★, exposure to which there are unsubstantiated hints of associations with cancer.
[d] MOPP, mechlorethamine, oncovin (vincristine), procarbazine, prednisone; UVA, ultraviolet-A; PUVA, psoralen (methoxsalen) + UVA radiation.
[e] The epidemiological data could not exclude mixed exposure to other phenoxyacetic acid herbicides; the association is stronger for mixed exposures.
[f] Probably due to exposures to organic solvents, especially benzene.
[g] Probably due to exposures to aromatic amines.
[h] ◆ for liver adenoma.
[i] The epidemiological data could not exclude mixed exposure to other chlorophenols; the association is stronger for mixed exposures.
[j] Mineral oils may vary in composition, particularly in the content of polycyclic organic materials, many of which are known to be carcinogenic in experimental animals.

le 3
icals and industrial exposure in humans

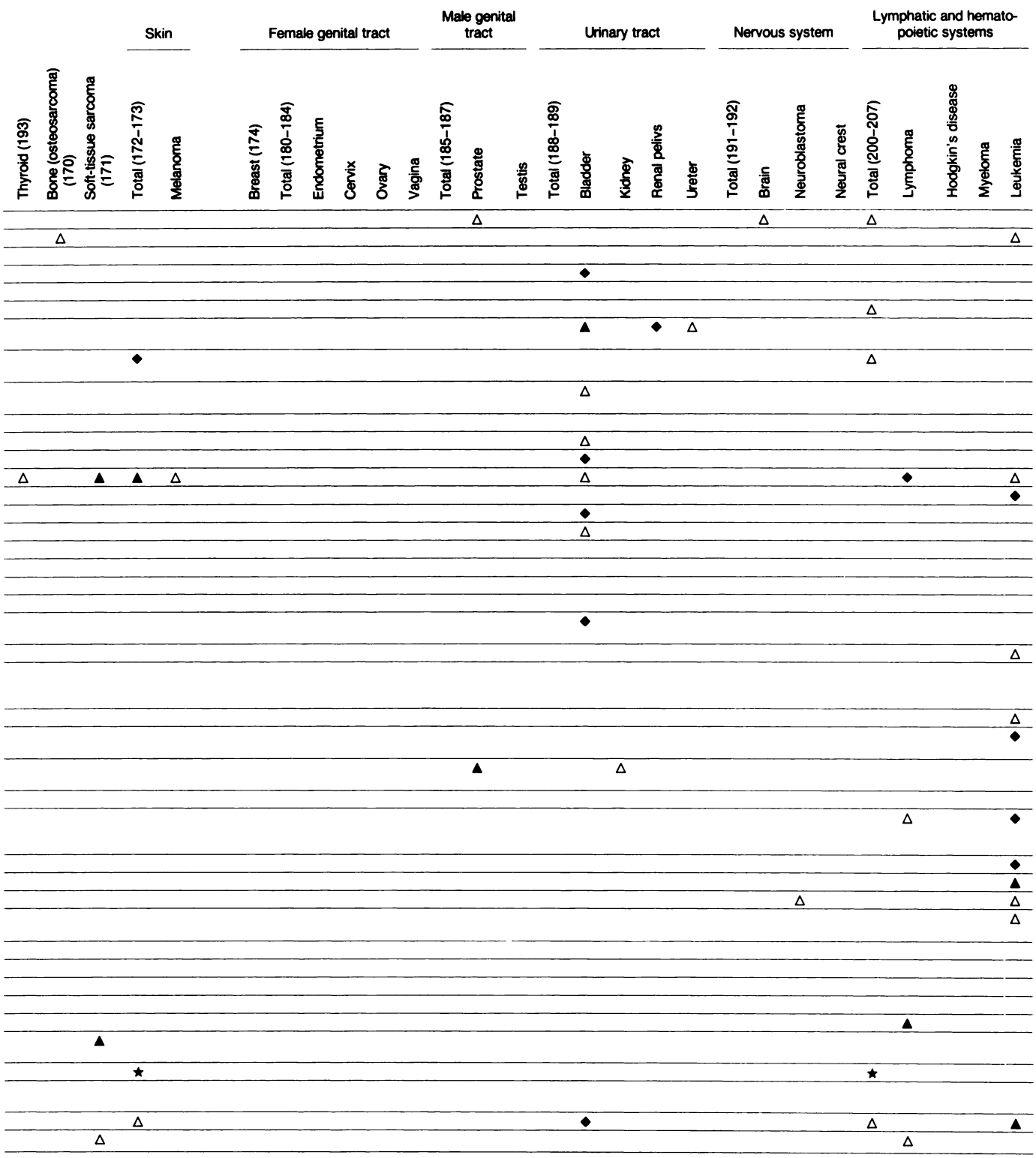
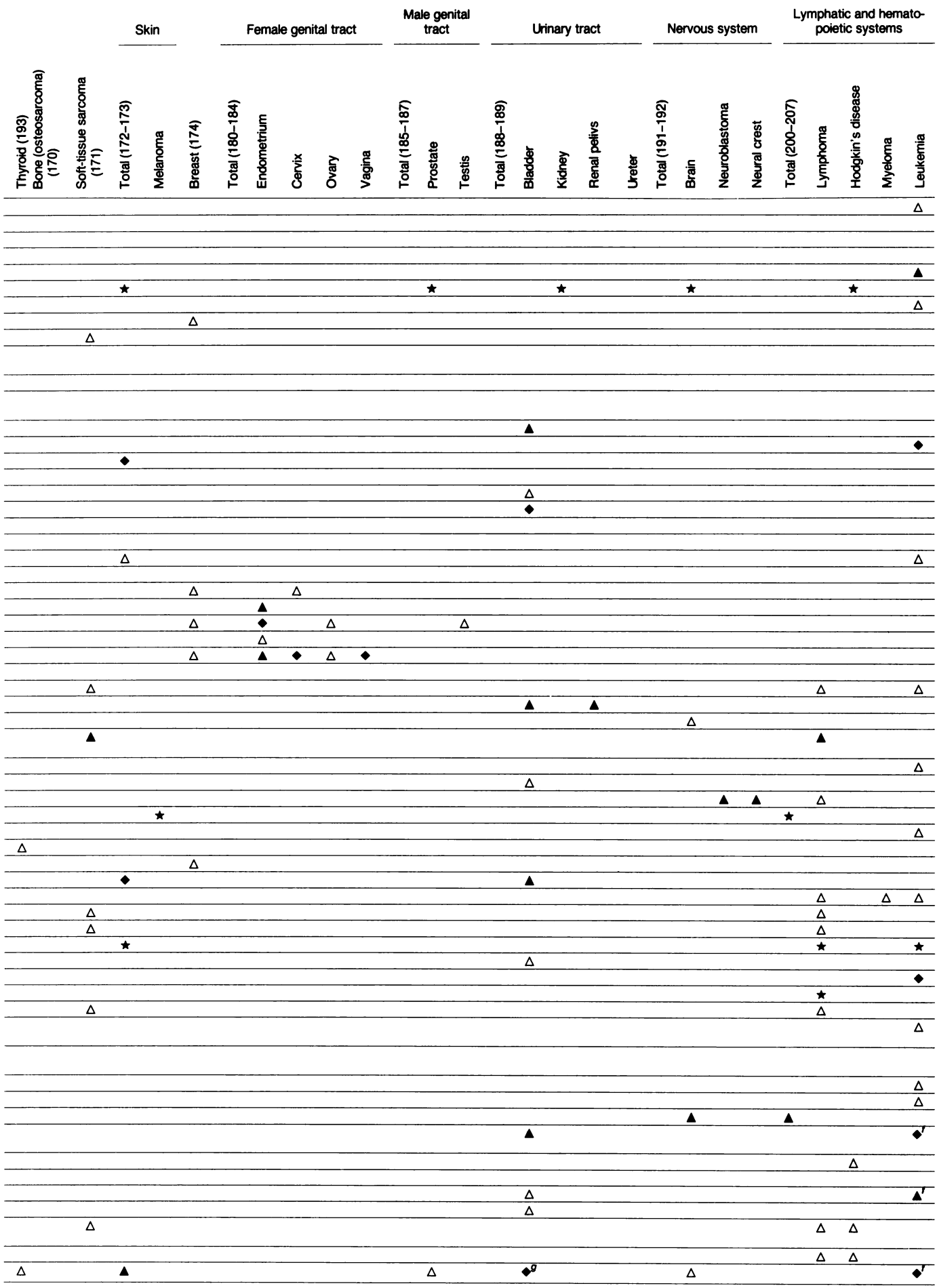


Table 3—

Chemical, process, or industry[a]	IARC Monographs ref. (volume and page)	Suppl. 4 ref. (page)	Oral cavity			Gastrointestinal tract					Liver				Nose and nasal sinus				
			Total (140–145)[b]	Salivary gland	Pharynx (146–149)	Total (150–154)	Esophagus	Stomach	Colon	Rectum	Total (155)	Antiosarcoma	Pancreas (157)	Peritoneum (mesothelioma) (158)	Total (160)	Adenocarcinoma	Larynx (161)	Lung, trachea and bronchus (162)	Pleural mesothelioma (163)
ortho- and *p*-Dichlorobenzenes	*29:* 213	108																	
Diethyl sulfate	*4:* 277	115															△		
Dimethyl sulfate	*4:* 271	119																▲	
Epichlorhydrin	*11:* 131	122																△	
Ethylene oxide	*11:* 157	126						△											
Formaldehyde gas	*29:* 345	131				★													
Hexachlorocyclohexanes	*20:* 195	133																	
Hydralazine	*24:* 85	135																	
Iron dextran complex (i.m. injection)	*2:* 161	145																	
Isonicotinic acid hydrazide (isoniazid)	*4:* 159	146																△	
Lead and lead compounds	*23:* 325	149																△	
Manufacture of isopropyl alcohol (strong-acid process)	*15:* 223	151													◆		▲		
Manufacture of magenta	*4:* 57	152																	
Melphalan	*9:* 167	154																	
Methoxsalen + UVA (PUVA)[d]	*24:* 101	158																	
Mustard gas	*9:* 181	163			△												▲	◆	
1-Naphthylamine	*4:* 87	164																	
2-Naphthylamine	*4:* 97	166																	
Nickel refining	*11:* 75	167													◆		▲	◆	
Nickel and nickel compounds	*11:* 75	167													▲		▲	▲	
Nitrogen mustard	*9:* 193	170																	
Estrogens and progestins																			
Combined p.o. contraceptives	*21:* 103	173									△[n]								
Sequential p.o. contraceptives	*21:* 111	177																	
Conjugated estrogens	*21:* 95	179																	
Dienestrol	*21:* 161	183																	
Diethylstilbestrol	*21:* 173	184																	
Oxymethalone	*13:* 131	203									▲								
Pentachlorophenols[f]	*20:* 303	205																	
Phenacetin	*24:* 135	47																	
Phenobarbital	*13:* 157	208																△	
Phenoxyacetic acid herbicides (occupational exposure to)	*15:* 111, 273	211																	
Phenylbutazone	*13:* 183	212																	
N-Phenyl-2-naphthylamine	*16:* 325	213																	
Phenytoin	*13:* 201	215																	
Polychlorinated biphenyls	*18:* 43	217				★					★		★						
Procarbazine	*26:* 311	220																	
Propyl thiouracil	*7:* 67	222																	
Reserpine	*24:* 211	222																	
Soots, tars, and some mineral oils[f]	*3:* 22	227				▲											▲	▲	
Styrene	*19:* 231	229																	
2,4,5-T and esters[e]	*15:* 273	235																	
Tetrachlorodibenzo-*p*-dioxin[e]	*15:* 41	238																	
Tetrachloroethylene	*20:* 491	243	★		★		★		★		★		★					★	
o-Toluidine	*27:* 155	245																	
Treosulfan	*26:* 341	246																	
Trichloroethylene	*20:* 545	247	★		★		★		★		★		★						
2,4,5- and 2,4,6-Trichlorophenols[f]	*20:* 349	249																	
Tris(1-aziridinyl)phosphine sulfide (thiotepa)	*9:* 85	252																	
Underground hematite mining (with exposure to radon)	*1:* 29	254																◆	
Vinblastine	*26:* 349	257																	
Vincristine	*26:* 365	259																	
Vinyl chloride	*19:* 377	260				▲						◆						▲	
Boot and shoe manufacture and repair	*25:* 249	138														◆			
Carpentry and joinery	*25:* 139	139		△											△				
Furniture and cabinet making	*25:* 99	140														◆		△	
Leather goods manufacture	*25:* 279	142																	
Leather tanning and processing	*25:* 201	142																	
Lumber and saw mills (including logging)	*25:* 49	143													△				
Pulp and paper manufacture	*25:* 157	144																	
Rubber manufacture	*28:*	144					△	▲	△				△					▲	

Continued



Limitations of the Epidemiological Studies. Whatever the criteria used, it should be appreciated that the amount of information currently available about target organs in humans depends not only on the number and size but also on the type of published epidemiological studies. Epidemiological studies have, like all other investigative methods, their own limitations. Some of these are quite general in nature and restrict the ability of such studies to detect an increase in risk for a cancer or to associate it clearly with exposure to a well-identified chemical. This may arise, for instance, because the exposure has been characterized only crudely in terms of broad occupational categories, and no actual measurements of the chemical have been made in the workplace environment, or because the groups under study are too small in size or have been followed up for insufficient time for an excess occurrence of a cancer to have been detected. More relevant to this paper, however, are limitations that may affect not only the general ability of a study to detect an increase in cancer risk, but the differential ability of a study to identify excess risks at different sites. For example, many of the available epidemiological studies are of the case-control type.

A case-control study is by its very nature focused on one or, less often, a few cancer sites and thus does not contribute information on possible associations of an exposure with cancer at all other sites. The sites not included may well be the commonest cancer sites, since case-control studies may be performed to investigate associations between relatively uncommon or rare cancers and exposures (a situation in which the case-control approach may be the only one practicable). Therefore, whether information can be obtained on exposure-cancer site associations from case-control studies depends heavily on the choice of sites made by the investigators.

Cohort studies cover instead, in principle, every cancer site; however, when several large cohorts are available, and a large spectrum of sites is examined, statistically significant associations with an exposure, due in fact to chance, may be encountered, which must be evaluated for consistency across cohorts before their causal implications can be accepted. Moreover, within one given cohort study, there is a greater probability of detecting as statistically significant an increase in relative risk for a frequent cancer (lung) than of detecting the same magnitude of increase for a rarer one (larynx). In general, and whatever the type of study, an investigator may decide to focus on a certain cancer site on the basis of previous suggestions of organ-specific carcinogenicity, thus reinforcing the selective character of the information available on exposure-cancer site associations.

Results

The results of the analysis are presented in Table 3, which is organized as a double-entry table with organs (systems) listed in the boxhead and chemicals in Column 1 of the table body. *Black diamonds* indicate those organ-chemical association(s) on which an evaluation of sufficient evidence of carcinogenicity rests. In reviewing and interpreting these associations, we adhered to a restrictive criterion, including only the most firmly established associations. For example, in the case of asbestos, only mesothelioma and lung cancer are included: for certain occupational exposures and industrial processes, like auramine manufacture, for which sufficient evidence of carcinogenicity exists for the process but not for the specific compound (auramine), only the former is denoted by a *black diamond*.

Black triangles are used to indicate target organ-chemical associations judged as possible or plausible to different degrees.

White triangles correspond to associations which were only suggested to exist for particular target organs.

In a number of other cases (*e.g.*, tetrachloroethylene), the available data provided unsubstantiated hints of associations of the exposure with cancer at many sites. This type of exposure is entered in Table 3 with a *star*.

Concluding Remarks

Although knowledge of factors like the distribution and biotransformation of environmental carcinogens may go some way to explaining the site specificity of some exposures in animals and in humans, in the greater majority of cases, the reasons for such specificity remain speculative. Indeed, the very concept of an absolute specificity (*i.e.*, of a qualitative difference in the susceptibility of different organs to a carcinogen), as opposed to a graded susceptibility of different organs and tissues, may be questionable. The basis for attributing a "site specificity" to a carcinogenic exposure in humans is an observable increase in risk, which, within the limits of the available studies (*e.g.*, in terms of sample size), can be detected only for certain sites. It is hoped that the product of the present exercise, namely, the table of established and possible associations between sites and chemicals, will help epidemiologists to sharpen their study hypotheses and to better delineate the site specificity of carcinogens in humans.

References

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vols. 1–31. Lyon: International Agency for Research on Cancer, 1971 to 1983.
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Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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